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T2R38 genotype is correlated with sinonasal quality of life in homozygous F508 cystic fibrosis patients

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Abstract

Background—Chronic rhinosinusitis (CRS) is very prevalent in the cystic fibrosis (CF) patient population, and leads to high morbidity and markedly decreased quality of life (QOL). Identification of genetic markers that contribute to CRS symptoms in these patients can allow for risk stratification and tailoring of medical and surgical treatments. T2R38 is a bitter taste receptor expressed in the sinonasal tract, and nonfunctional alleles of this receptor have been implicated in treatment-refractory CRS in non-CF patients. The purpose of this study is to investigate the significance of T2R38 genotype in the variability of sinonasal QOL and CRS disease severity in a sample of CF patients.

Methods— F508 homozygous CF patients were recruited from the University of Pennsylvania Cystic Fibrosis Center and were genotyped for the *TAS2R38* locus. To assess sinonasal symptom severity, a 22-item Sino-Nasal Outcome Test (SNOT-22) was collected from each patient. Additional demographic and medical history data was obtained at the time of patient enrollment.

Results—A total of 49 F508 homozygous CF patients aged 18 to 32 years were included in the final SNOT-22 score analysis. Individuals with 2 functional T2R38 alleles (PAV/PAV) had significantly lower SNOT-22 scores ($n = 49$, $p < 0.05$). On further breakdown of SNOT-22 subcategories, rhinologic symptoms specifically were less severe in PAV/PAV patients than patients with other genotypes ($n = 47$, $p < 0.05$).

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Conclusion—Our investigation indicates that T2R38 genotype correlates both with SNOT-22 scores and rhinologic-specific QOL in F508 homozygous CF patients.

Keywords

chronic rhinosinusitis; cystic fibrosis; T2R38; SNOT-22; bitter taste receptor; genetics

Cystic fibrosis (CF) is an autosomal recessive disorder that affects 30,000 people in the United States, and 70,000 people worldwide.¹ Patients suffer from the deleterious effects of CF on both lower and upper airway function, and opportunistic bacterial infections of the lung are the major cause of mortality in the disease.² There has been much advancement in the treatment of the pulmonary manifestations of CF over the past several decades, and patients are now living substantially longer lives.² With this increased lifespan, the morbidity of chronic rhinosinusitis (CRS) in CF has been recognized as increasingly important in patient quality of life (QOL). CRS affects close to one-half of all CF patients, with up to one-third of those affected ultimately needing sinus surgery for their disease.^{3–6} However, some patients remain relatively unaffected, suggesting that other disease modifiers play a role. The use of genetic markers to identify CF patients who will benefit most from tailored medical and surgical therapies for CRS can help improve QOL, while also eliminating unnecessary healthcare expense.

Although not all patients with CF report symptoms of CRS, computed tomography (CT) scans show the presence of sinonasal disease in up to 90% of patients.⁷ Additionally, over 80% of CF patients meet European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guidelines for the clinical diagnosis of CRS.⁸ However, symptom severity varies widely and initiation of treatment is based more on symptoms and QOL as opposed to radiologic evidence.⁹ The 22-item Sino-Nasal Outcome Test (SNOT-22) is a validated questionnaire for assessing symptoms associated with CRS, and it is helpful in assessing patient QOL. A recent study has validated its use in adults with CF as well, showing that the SNOT-22 is also able to effectively discriminate between patients with and without CRS.¹⁰

Although the CF phenotype presents with a variety of genotypes, F508 is by far the most common mutation.^{11,12} This is a deletion of 3 nucleotides that alters the cystic fibrosis transmembrane conductance regulator (CFTR) protein, causing aberrant folding and rapid degradation.¹ From 70% to 80% of individuals with CF are homozygous for the F508 mutation, and homozygotes are significantly younger at CF diagnosis, have poorer lung function, and have a higher early mortality rate than heterozygotes for F508, who make up a large proportion of the remainder of CF patients.¹² In addition to the F508 mutation, there are hundreds of other very rare mutations that can cause CF, with a very wide range of phenotypic severity.¹³

Evolving understanding of how biofilms impact CRS disease severity and treatment resistance involves the presence of bitter taste receptors in the respiratory tract. Acylhomoserine lactones (AHLs), produced by gram-negative bacteria, serve as biofilm “quorum-sensing molecules.” These molecules are also ligands for airway bitter taste chemoreceptors.¹⁴ It is thought that detection of AHLs before bacteria reach concentrations necessary for biofilm-formation allows an individual to mount an innate defensive response

prior to colonization or infection.¹⁵ One of these bitter taste receptors, T2R38, is activated by AHLs and has downstream effects of production of bactericidal nitric oxide (NO), which also increases ciliary beat frequency (CBF) and mucociliary clearance (MCC).¹⁶ The genetic locus for T2R38 has a balanced polymorphism in the white population yielding 2 primary alleles, with the functional allele containing the amino acids proline, alanine, and valine (PAV) and the nonfunctional allele containing alanine, valine, and isoleucine (AVI).¹⁶ Non-CF patients with a fully functional homozygote genotype (PAV/PAV) require significantly fewer sinus surgeries for CRS^{17,18} and harbor less gram-negative bacteria in the sinonasal cavity than non-PAV/PAV individuals.¹⁶

Correlation between the T2R38 genotype and recalcitrant CRS has not yet been investigated in CF patients. However, given the preponderance of *Pseudomonas aeruginosa* in CF patients, it is possible that variations in innate defense against *P. aeruginosa* biofilms may contribute to differences seen in lung and sinus pathology. Patients with a nonfunctional T2R38 allele may also have a “second hit” that predisposes them to increased infection. In the present investigation, we genotyped a population of F508 homozygous CF patients for T2R38 functionality, and investigated effects of genotype on SNOT-22 scores, need for functional endoscopic sinus surgery (FESS), and other patient characteristics, with the hypothesis that T2R38 genotype status will correlate with CRS disease severity in the CF patient.

Patients and methods

Patient selection

All patients were recruited through the University of Pennsylvania Cystic Fibrosis Center, with a confirmed CF diagnosis by DNA sequencing. Written consent was obtained for all participants, and the Institutional Review Board at the University of Pennsylvania approved all protocols. Patients were enrolled in the study starting on July 31, 2013, and the enrollment cutoff date for the current cross-sectional analysis was February 19, 2015.

Genotyping and SNOT-22

On the date of enrollment in the study, each patient gave a saliva sample from which genomic DNA was extracted, and T2R38 genotype was determined by allele-specific polymerase chain reaction (PCR), as described.^{16,17} In genotyping, patients were deidentified and personal information was recorded separately. Patients were also given a SNOT-22 form if they did not have a prior baseline SNOT-22 score, and all SNOT-22 scores were collected at the CF clinic during routine follow-up visits. The SNOT-22 is a validated tool for measuring the severity of symptoms related to CRS.¹⁹ Lower scores on the SNOT-22 (scale of 0 to 110) are highly correlated with reduced symptom severity and improved QOL.²⁰ If a patient failed to answer a question on their SNOT-22 questionnaire, that factor was excluded from their overall SNOT-22 score.

Additional data collection

Additional data was obtained in chart review and from the CF center database, including patient demographics, surgical history, infectious history, and imaging. Data was collected

retrospectively at the time of enrollment, and no prospective data was collected beyond the date of enrollment. To prevent bias, all data collectors were blinded to T2R38 genotype if it was known at the time of data acquisition. Information was not available in all patients for every factor examined.

General demographic information collected included age, gender, ethnicity, income, body mass index (BMI), and age at CF diagnosis. CF mutation type was also obtained from the CF center database. Other medical information, including a history of diabetes, asthma, allergies, nasal polyps, and infection with *P. aeruginosa* was included in the collection. Sputum cultures from all patients were collected to reflect the flora present in the respiratory tract of each individual. In support of sputum culture collection, there is substantial evidence in the literature demonstrating that lower airway cultures of cystic fibrosis patients are representative of the microbial community in the upper respiratory tract.^{21–23} Treatment modalities, such as current antibiotic courses, current steroid courses, nasal irrigations, previous sinus surgeries, and office visits with a diagnosis of sinusitis were also added to the data set. When available, CT scan and endoscopy results were recorded as well.

All study data was managed using the REDCap electronic data capture tool²⁴ hosted at the University of Pennsylvania.

Exclusion criteria

Only patients with a genotype of PAV/PAV, PAV/AVI, or AVI/AVI were considered in this analysis; individuals with a genotype of “other” or “unknown” were excluded. The F508 mutation accounts for approximately 70% of patients with CF,²⁵ and patients that were not homozygous for the F508 CF mutation were excluded to help limit outcome variability. The remaining patient population was used for initial data analysis.

Statistics

Stata 13 (Stata Statistical Software, College Station, TX) was used for all statistical analysis, with results shown as means $\pm$ standard deviation. All statistical tests used are clearly defined in the tables; a chi square test was used for all comparisons unless otherwise noted. A value of $p < 0.05$ was considered to be statistically significant.

Results

Between July 2013 and February 2015, 88 patients from the University of Pennsylvania Cystic Fibrosis Center were enrolled in the present study. Of these patients, 82 had a T2R38 genotype of PAV/PAV, PAV/AVI, or AVI/AVI; 6 individuals with “unknown” or “other” genotypes were excluded. These patients with “other” genotypes are expected to make up a minority of any patient population because there are several other rare haplotypes (such as AAV) that have not been thoroughly studied with regard to T2R38 function.²⁶ The F508 is the most common mutation in CF, and is a deletion of 3 nucleotides causing a loss of phenylalanine in CFTR, leading to abnormal protein folding and rapid degradation.¹ Of the remaining 82 patients, 69 were homozygous for the F508 CF mutation, and patients with other mutations were excluded to further limit variability in the study population.

SNOT-22 scores

A baseline SNOT-22 score was collected at a routine CF visit for all 69 patients to assess QOL and rhinologic symptom severity. To examine factors influencing the SNOT-22 results, we performed a bivariate analysis on several demographic, genetic, and medical variables and their relationship to SNOT-22 scores (Table 1). On initial descriptive statistics, the age-distribution was non-normal, with several older-age outliers. The 75th percentile cutoff for these 69 patients was age 33 years, so we examined the relationship of this age cutoff with SNOT-22 scores. There was a significant mean difference between SNOT-22 scores in those of age >32 years and those aged 18 to 32 years (mean difference -11.3 , $p < 0.05$, Wilcoxon rank-sum test). Because CF outcomes are very age-dependent and there may be several factors that cause the older group to be fundamentally different than our 18 to 32 years cohort, we attempted to control for age by a priori limiting further analysis to those in the 18 to 32 years age group. This made the age distribution normal, and made age differences less likely to confound results of a QOL comparison between genotypes.

SNOT-22 subgroup analysis of patients age 18 to 32 years

Of the 49 individuals aged 18 to 32 years, 7 (14%) had the PAV/PAV genotype, 18 (37%) had the AVI/AVI genotype, and the remaining 24 (49%) were heterozygotes (PAV/AVI). When controlling for age, diabetes status, BMI, and *P. aeruginosa* infection, PAV/PAV patients had significantly lower SNOT-22 scores than patients with a genotype of PAV/AVI or AVI/AVI (main effect of the predictor: 4.17 , $p < 0.05$, coefficient of -14.5 (range, -28.9 to -0.16), multivariate analysis of variance [ANOVA]).

To further investigate this protective effect, SNOT-22 scores were broken down into 5 symptom subcategories: rhinologic, extranasal, ear/facial, psychological, and sleep (Table 2). Each of these subcategories is made up of several questions from the SNOT-22 and each subcategory has been validated as a separate construct within the overall SNOT-22 score.²⁷ Forty-seven of the 49 patients had available subscores from intake; 2 patients had only a baseline score without subscore breakdown. Rhinologic symptoms were graded as significantly lower in PAV/PAV patients ($n = 7$, 2.7 ± 3.2) than non-PAV/PAV patients ($n = 41$, 8.9 ± 5.9) ($p < 0.05$, Mann-Whitney *U* test, 2-tailed). Scores for all other symptoms were consistently lower in PAV/PAV patients, but did not reach significance.

Other patient characteristics in age 18 to 32 years subgroup

Beyond the SNOT-22 score, we examined whether the T2R38 genotype would affect any of the other variables collected from the enrolled patients. These variables are shown in Table 3. The only factor that achieved significance was patient BMI, with AVI/AVI patients having a higher mean BMI (24 ± 3.5) than both heterozygous patients (21 ± 3.4) and PAV/PAV patients (22 ± 2.1) ($p < 0.05$, 1-way ANOVA). Lund-Mackay CT scoring and Lund-Kennedy endoscopic scores were available for too few patients to be included in any analysis. Notably, PAV/PAV patients trended toward less antibiotic use than non-PAV/PAV patients, but this result did not reach significance.

Discussion

The T2R38 bitter taste receptor has an emerging role in our understanding of innate immune defense against bacterial biofilm formation, and it has previously demonstrated a protective effect against the need for FESS in patients with CRS.¹⁸ CF patients, who have chronic mucus stasis, have both an increased sinonasal disease burden and higher incidence of CRS³ and demonstrate variability in responsiveness to medical and surgical treatment.²⁸ Based on these initial findings, F508 homozygous CF patients age 18 to 32 years who are homozygotes (PAV/PAV) for the functional T2R38 bitter taste receptor have significantly better rhinologic QOL as assessed by SNOT-22 than either the PAV/AVI or AVI/AVI patients. Furthermore, our subgroup analysis of rhinologic scores alone demonstrated an even greater statistical significance. Using the SNOT-22 in the CRS population has been validated as a QOL measurement, but in CF patients with multiple other significant comorbidities, such as lung disease, diabetes, and depression, rhinologic scores may only demonstrate higher correlation for otorhinolaryngologic manifestations.

Given the multiple contributory factors for both sinonasal disease burden and CRS in CF, we attempted to keep our population as homogenous as possible and only evaluate a single mutation cohort (F508 homozygous patients), as well as only those aged 18 to 32 years. In addition to creating a normal age distribution for our study data set, eliminating patients over age 32 years helps to control for any comorbid disease confounders or effect of genotype on longevity of CF patients. For example, if the PAV/PAV genotype truly confers a protective rhinologic phenotype, those patients may delay medical or surgical therapy and be overrepresented in older-aged CF patients, skewing the comparison of QOL measures.

Current literature identifies a number of factors that result in worsening CF phenotype including CF mutation status, BMI, sex, and age, but within those parameters, limited data has identified other genetic variable that may contribute to disease burden. That said, as of yet, only 1 non-CF mutation has been implicated in CF disease severity.²⁹

The implications of this study are broad. As discussed in the introductory section, the symptomatic rhinologic manifestations of CF are extremely broad. This data may help explain the varied manifestations. More importantly, this data further supports the role of T2R38 in airway innate defense and may have implications for stratifying risk for lower airway infections in this population.

One limitation of the current study is the smaller number of PAV/PAV patients. Although the study was adequately powered to detect differences in the ordinal data of the SNOT-22 assessment, differences in nominal data, such as “prior sinus surgery” or “current antibiotic use” are much more difficult to assess with a sample of this size. A larger, multi-institutional trial with T2R38 genotyping of CF patients would likely be necessary to distinguish these differences. Additionally, it is possible that patients with CF and CRS have an underrepresentation of the PAV/PAV genotype, because these individuals would theoretically be less likely to have symptoms of CRS warranting a primary diagnosis. The known population genotype distribution of northern European descent of PAV/PAV, PAV/AVI, and AVI/AVI is approximately 20%, 50%, and 30%, respectively,³⁰ so a larger sample would

also allow for detection of deviation from this distribution in the subset of CF patients. Additionally, heterozygotes (PAV/AVI) can predominately express either allele³¹; thus, as a group, they cannot be included with the PAV/PAV homozygote cohort without further molecular interrogation to determine if the functional allele is expressed at all and if so, to what degree.

Conclusion

Sinonasal infections and bacterial colonization likely lead to more serious pulmonary infections in patients with CF,⁸ and tailored medical and/or surgical therapy based on genetic markers may help to delay both sinonasal and pulmonary manifestations of the disease. This could potentially be accomplished with earlier medical therapy in those with higher risk genotypes, or in preventing unnecessary surgical intervention in those who would not be expected to benefit. Patients with a PAV/PAV genotype for functional alleles of the T2R38 bitter taste receptor have a significantly improved self-assessment of sinonasal symptoms compared to patients of other genotypes and may help explain the differences in both rhinologic QOL and CRS manifestations in the CF population. The use of T2R38 as a genetic marker in CF patients offers a novel approach to evaluation of sinonasal disease in this population and may ultimately help in future treatment modalities.

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TABLE 1

Factors influencing sinonasal outcomes in all patients (n = 69) *

Predictors	SNOT-22 mean difference (<i>p</i>)
Male vs female	−2.9 (0.51)
Family income \$90 k vs <\$90 k	0.9 (0.87)
PAV/PAV vs not	−6.2 (0.29)
AVI/AVI vs not	1.7 (0.72)
Age (18–32 vs 33)	−11.3 (0.02)
Diabetic vs not	−1.2 (0.80)
BMI (22 vs <22)	2.2 (0.63)
Current <i>P. aeruginosa</i> infection vs none	3.0 (0.74)

* All mean differences calculated using the Wilcoxon rank sum test. Bold values are significant.

AVI = nonfunctional allele containing alanine, valine, and isoleucine; BMI = body mass index; PAV = functional allele containing the amino acids proline, alanine, and valine; SNOT-22 = 22-item Sino-Nasal Outcome Test.

TABLE 2

Genotype effect on SNOT-22 subcategory scores in patients aged 18 to 32 years (n = 47) *

Symptom subtype	PAV/PAV	Non-PAV/PAV	<i>p</i> ^a
Rhinologic score	2.7 ± 3.2	8.9 ± 5.9	0.01 (U = 224)
Extranasal score	4.6 ± 4	5.8 ± 3.9	0.40 (U = 169)
Ear/facial score	2.3 ± 1.9	3.9 ± 3.9	0.45 (U = 166)
Psychological score	3.3 ± 2.2	6.3 ± 6.5	0.47 (U = 165)
Sleep score	3.7 ± 2.7	7.9 ± 7.5	0.30 (U = 176)

* Values are mean difference ± standard deviation.

^a Significance calculated using Mann-Whitney *U* test, 2-tailed (n₁ = 7; n₂ = 40).

Bold values are significant.

PAV = functional allele containing the amino acids proline, alanine, and valine; SNOT-22 = 22-item Sino-Nasal Outcome Test.

TABLE 3

T2R38 distribution of additional factors in age group 18 to 32 years *

	AVI/AVI	AVI/PAV	PAV/PAV	p
Total patients, n (%)	18 (37)	24 (49)	7 (14)	
Demographics				
Male, n (%)	8 (44)	14 (58%)	4 (57)	0.92
Age (years), mean $\pm$ SD ^a	26.5 $\pm$ 3	25 $\pm$ 3	25 $\pm$ 3	0.99
White, n (%)	18 (100%)	24 (100%)	6 (86)	
Age at CF diagnosis (days), median ^b	180	90	360	0.12
BMI, mean $\pm$ SD ^a	24 $\pm$ 3.5	21 $\pm$ 3.4	22 $\pm$ 2.1	0.02
Other rhinologic symptoms				
Polyps (n = 22) ^c	2	7	1	0.67
Asthma, n (%) ^c	9 (50)	12 (50)	5 (71)	0.58
Environmental allergy symptoms, n (%)	7 (39)	17 (71)	4 (57)	0.12
Other medical conditions				
Medication allergy symptoms, n (%)	5 (28)	7 (29)	1 (14)	0.82
Diabetes, n (%)	8 (44)	11 (46)	6 (86)	0.16
HbA1c, median ^b	5.8	5.8	7.2	0.84
Current <i>P. aeruginosa</i> infection, n (%)	14 (78)	17 (71)	4 (57)	0.57
Treatment				
On current antibiotics, n (%)	14 (82)	18 (86)	3 (50)	0.22
On current antibiotics (PAV/PAV vs non-PAV/PAV), n (%) ^c	32 (84)		3 (50)	0.09
On current steroid course, n (%) ^c	1 (6)	3 (14)	2 (33)	0.21
On current nasal irrigation, n (%) ^c	7 (41)	5 (24)	1 (17)	0.44
Previous sinus surgery, n (%)	8 (44)	7 (29)	1 (14)	0.54
Previous sinus surgery (PAV/PAV vs non-PAV/PAV), n (%) ^c	15 (38)		1 (14)	0.40
Surgeries (if previous surgeries), mean $\pm$ SD**	2.5 $\pm$ 2.1	2.9 $\pm$ 1.8)	1	0.72
Need for >1 sinus surgery (PAV/PAV vs non-PAV/PAV), n (%) ^c	9 (21)		0 (0)	0.32

* All statistical tests are chi square except those indicated in footnotes a, b, and c. Percentages are based on the number of individuals in each group who had data available for the factor in question (total "n" may be <49 for some variables).

^aOne-way ANOVA.

^bMood's median test.

^cFisher's exact test.

ANOVA = analysis of variance; AVI = nonfunctional allele containing alanine, valine, and isoleucine; BMI = body mass index; CF = cystic fibrosis; HbA1c = glycosylated hemoglobin A1c; PAV = functional allele containing the amino acids proline, alanine, and valine; SD = standard deviation.

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